Supporting Information

Supplementary Tables 1-5

Table S1 Human structural E2-E3 interaction network constructed by Prism algorithm

First and second columns list the E3 and E2 proteins, respectively, which are predicted to be interacting by Prism. In the third column, the corresponding template interface which is used to make the prediction is shown. In the fourth column, literature reference is given if the interaction has been reported in earlier studies.

Target protein 1 (E3)	Target protein 2 (E2)	Template name	Literature reference
Birc3 (3eb6:A)	UBE2D2 (3eb6:B)	3eb6:AB	Ref. [1] (PDB)
Birc3 (3eb6:A)	UBE2E1 (3bzh:A)	3eb6:AB	Ref. [2]
Brca1 (1jm7:A)	UBE2B (1jas)	3eb6:AB	
Brca1 (1jm7:A)	UBE2I (2grn:A)	3eb6:AB	Ref. [3]
Brca1 (1jm7:A)	UBE2N (3hcu:B)	3eb6:AB	Ref. [4]
c-Cbl (1fbv:A)	UBE2B (1jas)	1fbv:AC	
c-Cbl (1fbv:A)	UBE2D1 (2c4p:A)	1ur6:AB	Ref. [5]
c-Cbl (1fbv:A)	UBE2D2 (1ur6:A)	1ur6:AB	Ref. [6]
c-Cbl (1fbv:A)	UBE2D3 (1x23:A)	1ur6:AB	Ref. [7]
c-Cbl (1fbv:A)	UBE2E1 (3bzh)	1fbv:AC	Ref. [8]
c-Cbl (1fbv:A)	UBE2E2 (1y6l:A)	1ur6:AB	
c-Cbl (1fbv:A)	UBE2H (2z5d:A)	1ur6:AB	
c-Cbl (1fbv:A)	UBE2K (1yla:A)	1ur6:AB	
c-Cbl (1fbv:A)	UBE2L3 (1fbv:C)	1fbv:AC	Ref. [9] (PDB)
c-Cbl (1fbv:A)	UBE2L6 (2kjh:A)	1ur6:AB	
c-Cbl (1fbv:A)	UBE2N (3hct:B)	1fbv:AC	
c-Cbl (1fbv:A)	UBE2Q2 (1zuo:A)	1ur6:AB	
Huwe1 (3g1n:A)	UBE2C (1i7k:A)	3jw0:AC	
Huwe1 (3g1n:A)	UBE2D1 (2c4p:A)	1c4z:AD	Ref. [10]
Huwe1 (3g1n:A)	UBE2D2 (1ur6:A)	1c4z:AD	
Huwe1 (3g1n:A)	UBE2D3 (1x23:A)	1c4z:AD	
Huwe1 (3g1n:A)	UBE2J2 (2f4w:A)	3jw0:AC	
Huwe1 (3g1n:A)	UBE2L6 (2kjh:A)	1c4z:AD	
Mdm2 (2hdp:A)	UBE2D1 (2c4p:A)	1ur6:AB	Ref. [11]
Mdm2 (2hdp:A)	UBE2D2 (3jw0:B)	1ur6:AB	Ref. [11]
Mdm2 (2hdp:A)	UBE2D3 (1x23:A)	1ur6:AB	Ref. [11]
Mdm2 (2vje:A)	UBE2E1 (3bzh)	1ur6:AB	
Mdm2 (2vje:A)	UBE2G2 (3h8k:A)	1ur6:AB	Ref. [12]
Mdm2 (2vje:A)	UBE2L6 (2kjh:A)	1ur6:AB	
Mdm2 (2hdp:A)	UBE2M (2nvu:C)	1ur6:AB	
Nedd4l (3jw0:D)	UBE2B (1jas)	1c4z:AD	
Nedd4l (3jvz:D)	UBE2D1 (2c4p:A)	1c4z:AD	Ref. [13]
Nedd4l (3jw0:D)	UBE2D2 (3jw0:B)	3jw0:BD	Ref. [14] (PDB)
Nedd4l (3jvz:D)	UBE2I (2grn:A)	3jw0:AC	

Nedd4l (3jvz:D)	UBE2J2 (2f4w:A)	3jvz:AC	
Nedd4l (3jw0:D)	UBE2L3 (1c4z:D)	3jw0:AC	Ref. [15]
Nedd4l (3jvz:D)	UBE2L6 (2kjh:A)	1c4z:AD	
Nedd4l (3jvz:D)	UBE2R1 (2ob4)	1c4z:AD	
Rbx1 (3dpl:R)	UBE2H (2z5d:A)	1ur6:AB	
Rbx1 (3dpl:R)	UBE2M (2nvu:C)	1ur6:AB	Ref. [8]
Rbx1 (3dpl:R)	UBE2N (3hcu:B)	1ur6:AB	
Rbx1 (3dpl:R)	UBE2S (1zdn:A)	1ur6:AB	
Rbx2 (2ecl)	UBE2D1 (2c4p:A)	1ur6:AB	Ref. [8]
Rbx2 (2ecl)	UBE2E2 (1y6l:A)	1ur6:AB	
Rbx2 (2ecl)	UBE2G1 (2awf)	1ur6:AB	
Rbx2 (2ecl)	UBE2K (1yla:A)	1ur6:AB	
Rbx2 (2ecl)	UBE2L3 (1fbv:C)	1ur6:AB	
Rbx2 (2ecl)	UBE2N (3hcu:B)	1ur6:AB	
Rbx2 (2ecl)	UBE2S (1zdn:A)	1ur6:AB	
Smurf2 (1zvd)	UBE2B (1jas)	3jw0:AC	
Smurf2 (1zvd)	UBE2C (1i7k:A)	3jw0:AC	
Smurf2 (1zvd)	UBE2D1 (2c4p:A)	1c4z:AD	Ref. [16]
Smurf2 (1zvd)	UBE2D2 (1ur6:A)	3jvz:AC	Ref. [17]
Smurf2 (1zvd)	UBE2H (2z5d:A)	1c4z:AD	
Smurf2 (1zvd)	UBE2I (2grn:A)	1c4z:AD	
Smurf2 (1zvd)	UBE2J2 (2f4w:A)	1c4z:AD	
Smurf2 (1zvd)	UBE2L3 (1fbv:C)	3jw0:AC	Ref. [18]
Smurf2 (1zvd)	UBE2L6 (2kjh:A)	1c4z:AD	
Smurf2 (1zvd)	UBE2M (2nvu:C)	3jw0:AC	
Traf6 (2eci)	UBE2B (1jas)	3hct:AB	
Traf6 (2eci)	UBE2C (1i7k:A)	3hct:AB	
Traf6 (2eci)	UBE2D2 (1ur6:A)	2oxq:AC	Ref. [8]
Traf6 (2jmd)	UBE2D3 (1x23:A)	3hct:AB	Ref. [19]
Traf6 (2jmd)	UBE2F (3fn1:B)	3hct:AB	
Traf6 (2eci)	UBE2G2 (3h8k:A)	3hct:AB	
Traf6 (2jmd)	UBE2H (2z5d:A)	3hct:AB	
Traf6 (2jmd)	UBE2J2 (2f4w:A)	3hct:AB	
Traf6 (3hct:A)	UBE2K (1yla:A)	3eb6:AB	
Traf6 (2jmd)	UBE2L3 (1fbv:C)	2oxq:AC	Ref. [20]
Traf6 (3hct:A)	UBE2L6 (2kjh:A)	3hct:AB	
Traf6 (3hct:A)	UBE2N (3hct:B)	3hct:AB	Ref. [21] (PDB)
Traf6 (2jmd)	UBE2Q1 (2qgx:A)	1ur6:AB	
Trim37 (3lrq:A)	UBE2D2 (1ur6:A)	1ur6:AB	Ref. [22]
Ube3a (1c4z:A)	UBE2B (1jas)	1c4z:AD	
Ube3a (1c4z:A)	UBE2C (1i7k:A)	1c4z:AD	
Ube3a (1c4z:A)	UBE2D1 (2c4p:A)	1c4z:AD	Ref. [15]
Ube3a (1c4z:A)	UBE2D2 (3jw0:B)	1c4z:AD	Ref. [23]
Ube3a (1d5f:A)	UBE2D3 (1x23:A)	1c4z:AD	Ref. [24]
Ube3a (1c4z:A)	UBE2E2 (1y6l:A)	1c4z:AD	
Ube3a (1d5f:A)	UBE2F (3fn1:B)	1c4z:AD	
Ube3a (1c4z:A)	UBE2G2 (3h8k:A)	1c4z:AD	Ref. [25]
Ube3a (1c4z:A)	UBE2I (2grn:A)	1c4z:AD	Ref. [26]

Ube3a (1c4z:A)	UBE2J2 (2f4w:A)	1c4z:AD	
Ube3a (1c4z:A)	UBE2K (1yla:A)	1c4z:AD	
Ube3a (1c4z:A)	UBE2L3 (1c4z:D)	1c4z:AD	Ref. [27] (PDB)
Ube3a (1d5f:A)	UBE2L6 (2kjh:A)	1c4z:AD	Ref. [27]
Ube3a (1c4z:A)	UBE2M (2nvu:C)	1c4z:AD	
Ube3a (1c4z:A)	UBE2N (3hcu:B)	1c4z:AD	
Ube3a (1d5f:A)	UBE2Q2 (1zuo:A)	1c4z:AD	
Ube3a (1d5f:A)	UBE2R1 (2ob4)	1c4z:AD	
Ube4a (1wgm)	UBE2G2 (3h8k:A)	2oxq:AC	
Ube4a (1wgm)	UBE2N (3hcu:B)	2oxq:AC	
Ube4b (3l1z:B)	UBE2D3 (3l1z:A)	3l1z:AB	Ref. [28] (PDB)
Wwp1 (1nd7)	UBE2B (1jas)	3jw0:AC	
Wwp1 (1nd7)	UBE2C (1i7k:A)	1c4z:AD	
Wwp1 (1nd7)	UBE2D2 (1ur6:A)	1c4z:AD	
Wwp1 (1nd7)	UBE2E2 (1y6l:A)	1c4z:AD	
Wwp1 (1nd7)	UBE2F (3fn1:B)	1c4z:AD	
Wwp1 (1nd7)	UBE2G2 (3h8k:A)	3jvz:AC	
Wwp1 (1nd7)	UBE2H (2z5d:A)	3jvz:AC	
Wwp1 (1nd7)	UBE2K (1yla:A)	1c4z:AD	
Wwp1 (1nd7)	UBE2N (3hct:B)	3jw0:AC	
Wwp1 (1nd7)	UBE2R1 (2ob4)	1c4z:AD	
Xiap (2ecg)	UBE2D2 (3jw0:B)	3eb6:AB	Ref. [8]
Xiap (2ecg)	UBE2D3 (1x23:A)	3eb6:AB	Ref. [8]
Xiap (2ecg)	UBE2E1 (3bzh)	3eb6:AB	Ref. [29]
Xiap (2ecg)	UBE2E2 (1y6l:A)	3eb6:AB	Ref. [8]

Table S2 Interface and hotspot residues on α-helix 1, loop L1 and L2 regions of E2s interacting with E3s.

For each E3 protein ligase, E2 partners and interface region on E2s are shown. Interface and hotspot residues are determined by Hotpoint server [30]. Structure-based multiple sequence alignment of human E2s are obtained from Christensen et al. [31] and along with this representation, interface residues and hot spot residues are displayed in blue and red color, respectively.

Mdm2 (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2D1	UbcH5a	1 MA-LKRIQKELSDLQRD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D3	UbcH5c	1 MA-LKRINKELSDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2E1	UbcH6	47 TS-AKRIQKELADITLD	:103 TPEYPFKPP	:137 DN----------WSPA----------LT
UBE2G2	Ubc7	4 TA-LKRLMAEYKQLTLN	:61 PLDYPLSPP	:108 ER----------WSPV----------QS
UBE2L6	UbcH8	1 MA-SMRVVKELEDLQKK	:57 PPEYPFKPP	:92 EN----------WKPC----------TK
UBE2M	Ubc12	28 SAAQLRIQKDINELNL-	:83 GQGYPHDPP	:117 ED----------WKPV----------LT

Rbx1 (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2H	UbcH2	24 SPGKRRMDTDVVKLIES	:77 PDKYPFKSP	:112 QT----------WTAL----------YD
UBE2M	Ubc12	28 SAAQLRIQKDINELNL-	:83 GQGYPHDPP	:117 ED----------WKPV----------LT
UBE2N	Ubc13	2 AGLPRRIIKETQRLLAE	:59 PEEYPMAAP	:93 DK----------WSPA----------LQ
UBE2S		10 PH-IIRLVYKEVTTLTA	:67 GKDFPASPP	:101 RD----------WTAE----------LG

Rbx2 (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2D1	UbcH5a	1 MA-LKRIQKELSDLQRD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2E2		1 TS-AKRIQKELAEITLD	:57 SPDYPFKPP	:91 DN----------WSPA----------LT
UBE2G1	Ubc7	5 QS-ALLLRRQLAELNKN	:62 PKDYPLRPP	:109 ER----------WLPI----------HT
UBE2K	E2-25K	3 NIAVQRIKREFKEVLKS	:63 PETYPFNPP	:98 DQ----------WAAA----------MT
UBE2L3	UbcH7	1 MAASRRLMKELEEIRKC	:58 PAEYPFKPP	:93 EN----------WKPA----------TK
UBE2N	Ubc13	2 AGLPRRIIKETQRLLAE	:59 PEEYPMAAP	:93 DK----------WSPA----------LQ
UBE2S		10 PH-IIRLVYKEVTTLTA	:67 GKDFPASPP	:101 RD----------WTAE----------LG

c-Cbl (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2B	Rad6b	3 TPARRRLMRDFKRLQED	:60 SEEYPNKPP	:94 NR----------WSPT----------YD
UBE2D1	UbcH5a	1 MA-LKRIQKELSDLQRD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D3	UbcH5c	1 MA-LKRINKELSDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2E1	UbcH6	47 TS-AKRIQKELADITLD	:103 TPEYPFKPP	:137 DN----------WSPA----------LT
UBE2E2		1 TS-AKRIQKELAEITLD	:57 SPDYPFKPP	:91 DN----------WSPA----------LT
UBE2H	UbcH2	24 SPGKRRMDTDVVKLIES	:77 PDKYPFKSP	:112 QT----------WTAL----------YD
UBE2K	E2-25K	3 NIAVQRIKREFKEVLKS	:63 PETYPFNPP	:98 DQ----------WAAA----------MT
UBE2L3	UbcH7	1 MAASRRLMKELEEIRKC	:58 PAEYPFKPP	:93 EN----------WKPA----------TK
UBE2L6	UbcH8	1 MA-SMRVVKELEDLQKK	:57 PPEYPFKPP	:92 EN----------WKPC----------TK
UBE2N	Ubc13	2 AGLPRRIIKETQRLLAE	:59 PEEYPMAAP	:93 DK----------WSPA----------LQ
UBE2Q2		203 VQASDRLMKELRDIYRS	:275 KDNFPFDPP	:311 QG----------WSSA----------YS

Birc3 (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2E1	UbcH6	47 TS-AKRIQKELADITLD	:103 TPEYPFKPP	:137 DN----------WSPA----------LT

Brca1 (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2B	Rad6b	3 TPARRRLMRDFKRLQED	:60 SEEYPNKPP	:94 NR----------WSPT----------YD
UBE2I	Ubc9	4 -IALSRLAQERKAWRKD	:65 KDDYPSSPP	:101 KD----------WRPA----------IT
UBE2N	Ubc13	2 AGLPRRIIKETQRLLAE	:59 PEEYPMAAP	:93 DK----------WSPA----------LQ

Xiap (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D3	UbcH5c	1 MA-LKRINKELSDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2E1	UbcH6	47 TS-AKRIQKELADITLD	:103 TPEYPFKPP	:137 DN----------WSPA----------LT
UBE2E2		1 TS-AKRIQKELAEITLD	:57 SPDYPFKPP	:91 DN----------WSPA----------LT

Trim37 (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT

Traf6 (RING-finger E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2B	Rad6b	3 TPARRRLMRDFKRLQED	:60 SEEYPNKPP	:94 NR----------WSPT----------YD
UBE2C	UbcH10	29 GPVGKRLQQELMTLMMS	:86 PSGYPYNAP	:120 EK----------WSAL----------YD
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D3	UbcH5c	1 MA-LKRINKELSDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2F		31 SVRDKLLVKEVAELEAN	:88 PDAYNMVPP	:128 TG----------WAPT----------RT
UBE2G2	Ubc7	4 TA-LKRLMAEYKQLTLN	:61 PLDYPLSPP	:108 ER----------WSPV----------QS
UBE2H	UbcH2	24 SPGKRRMDTDVVKLIES	:77 PDKYPFKSP	:112 QT----------WTAL----------YD
UBE2J2		11 TTATQRLKQDYLRIKKD	:68 PREFPFKPP	:93 LCLSITDFHPDTWNPA----------WS
UBE2K	E2-25K	3 NIAVQRIKREFKEVLKS	:63 PETYPFNPP	:98 DQ----------WAAA----------MT
UBE2L3	UbcH7	1 MAASRRLMKELEEIRKC	:58 PAEYPFKPP	:93 EN----------WKPA----------TK
UBE2L6	UbcH8	1 MA-SMRVVKELEDLQKK	:57 PPEYPFKPP	:92 EN----------WKPC----------TK
UBE2N	Ubc13	2 AGLPRRIIKETQRLLAE	:59 PEEYPMAAP	:93 DK----------WSPA----------LQ
UBE2Q1		3 VQATDRLMKELRDIYRS	:75 KDNFPFDPP	:111 QG----------WSSA----------YS

Huwe1 (HECT E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2C	UbcH10	29 GPVGKRLQQELMTLMMS	:86 PSGYPYNAP	:120 EK----------WSAL----------YD
UBE2D1	UbcH5a	1 MA-LKRIQKELSDLQRD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D3	UbcH5c	1 MA-LKRINKELSDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2J2		11 TTATQRLKQDYLRIKKD	:68 PREFPFKPP	:93 LCLSITDFHPDTWNPA----------WS
UBE2L6	UbcH8	1 MA-SMRVVKELEDLQKK	:57 PPEYPFKPP	:92 EN----------WKPC----------TK

Nedd4l (HECT E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2B	Rad6b	3 TPARRRLMRDFKRLQED	:60 SEEYPNKPP	:94 NR----------WSPT----------YD
UBE2D1	UbcH5a	1 MA-LKRIQKELSDLQRD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2I	Ubc9	4 -IALSRLAQERKAWRKD	:65 KDDYPSSPP	:101 KD----------WRPA----------IT
UBE2J2		11 TTATQRLKQDYLRIKKD	:68 PREFPFKPP	:93 LCLSITDFHPDTWNPA----------WS
UBE2L3	UbcH7	1 MAASRRLMKELEEIRKC	:58 PAEYPFKPP	:93 EN----------WKPA----------TK
UBE2L6	UbcH8	1 MA-SMRVVKELEDLQKK	:57 PPEYPFKPP	:92 EN----------WKPC----------TK
UBE2R1	Cdc34	10 ---QKALLLELKGLQEE	:65 PIDYPYSPP	:97 -L----------HPPVDDPQSGELPSERWNPTQN

Wwp1 (HECT E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2B	Rad6b	3 TPARRRLMRDFKRLQED	:60 SEEYPNKPP	:94 NR----------WSPT----------YD
UBE2C	UbcH10	29 GPVGKRLQQELMTLMMS	:86 PSGYPYNAP	:120 EK----------WSAL----------YD
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2E2		1 TS-AKRIQKELAEITLD	:57 SPDYPFKPP	:91 DN----------WSPA----------LT
UBE2F		31 SVRDKLLVKEVAELEAN	:88 PDAYNMVPP	:128 TG----------WAPT----------RT
UBE2G2	Ubc7	4 TA-LKRLMAEYKQLTLN	:61 PLDYPLSPP	:108 ER----------WSPV----------QS
UBE2H	UbcH2	24 SPGKRRMDTDVVKLIES	:77 PDKYPFKSP	:112 QT----------WTAL----------YD
UBE2K	E2-25K	3 NIAVQRIKREFKEVLKS	:63 PETYPFNPP	:98 DQ----------WAAA----------MT
UBE2N	Ubc13	2 AGLPRRIIKETQRLLAE	:59 PEEYPMAAP	:93 DK----------WSPA----------LQ
UBE2R1	Cdc34	10 ---QKALLLELKGLQEE	:65 PIDYPYSPP	:97 -L----------HPPVDDPQSGELPSERWNPTQN

Smurf2 (HECT E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2B	Rad6b	3 TPARRRLMRDFKRLQED	:60 SEEYPNKPP	:94 NR----------WSPT----------YD
UBE2C	UbcH10	29 GPVGKRLQQELMTLMMS	:86 PSGYPYNAP	:120 EK----------WSAL----------YD
UBE2D1	UbcH5a	1 MA-LKRIQKELSDLQRD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2H	UbcH2	24 SPGKRRMDTDVVKLIES	:77 PDKYPFKSP	:112 QT----------WTAL----------YD
UBE2I	Ubc9	4 -IALSRLAQERKAWRKD	:65 KDDYPSSPP	:101 KD----------WRPA----------IT
UBE2J2		11 TTATQRLKQDYLRIKKD	:68 PREFPFKPP	:93 LCLSITDFHPDTWNPA----------WS
UBE2L3	UbcH7	1 MAASRRLMKELEEIRKC	:58 PAEYPFKPP	:93 EN----------WKPA----------TK
UBE2L6	UbcH8	1 MA-SMRVVKELEDLQKK	:57 PPEYPFKPP	:92 EN----------WKPC----------TK
UBE2M	Ubc12	28 SAAQLRIQKDINELNL-	:83 GQGYPHDPP	:117 ED----------WKPV----------LT

Ube3a (HECT E3) interactions

E2 symbol	E2 Common name	Helix-1	Loop L1	Loop L2
UBE2B	Rad6b	3 TPARRRLMRDFKRLQED	:60 SEEYPNKPP	:94 NR----------WSPT----------YD
UBE2C	UbcH10	29 GPVGKRLQQELMTLMMS	:86 PSGYPYNAP	:120 EK----------WSAL----------YD
UBE2D1	UbcH5a	1 MA-LKRIQKELSDLQRD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D2	UbcH5b	1 MA-LKRIHKELNDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2D3	UbcH5c	1 MA-LKRINKELSDLARD	:57 PTDYPFKPP	:91 SQ----------WSPA----------LT
UBE2E2		1 TS-AKRIQKELAEITLD	:57 SPDYPFKPP	:91 DN----------WSPA----------LT
UBE2F		31 SVRDKLLVKEVAELEAN	:88 PDAYNMVPP	:128 TG----------WAPT----------RT
UBE2G2	Ubc7	4 TA-LKRLMAEYKQLTLN	:61 PLDYPLSPP	:108 ER----------WSPV----------QS
UBE2I	Ubc9	4 -IALSRLAQERKAWRKD	:65 KDDYPSSPP	:101 KD----------WRPA----------IT
UBE2J2		11 TTATQRLKQDYLRIKKD	:68 PREFPFKPP	:93 LCLSITDFHPDTWNPA----------WS
UBE2K	E2-25K	3 NIAVQRIKREFKEVLKS	:63 PETYPFNPP	:98 DQ----------WAAA----------MT

UBE2L3	UbcH7	1	MAASRRLMKELEEIRKC	:58	PAEYPFKPP	:93	EN----------WKPA----------TK
UBE2L6	UbcH8	1	MA-SMRVVKELEDLQKK	:57	PPEYPFKPP	:92	EN----------WKPC----------TK
UBE2M	Ubc12	28	SAAQLRIQKDINELNL-	:83	GQGYPHDPP	:117	ED----------WKPV----------LT
UBE2N	Ubc13	2	AGLPRRIIKETQRLLAE	:59	PEEYPMAAP	:93	DK----------WSPA----------LQ
UBE2Q2		203	VQASDRLMKELRDIYRS	:275	KDNFPFDPP	:311	QG----------WSSA----------YS
UBE2R1	Cdc34	10	---QKALLLELKGLQEE	:65	PIDYPYSPP	:97	-L----------HPPVDDPQSGELPSERWNPTQN

Ube4a (U-box E3) interactions

E2 symbol	E2 Common name		Helix-1		Loop L1		Loop L2
UBE2G2	Ubc7	4	TA-LKRLMAEYKQLTLN	:61	PLDYPLSPP	:108	ER----------WSPV----------QS
UBE2N	Ubc13	2	AGLPRRIIKETQRLLAE	:59	PEEYPMAAP	:93	DK----------WSPA----------LQ

Ube4b (U-box E3) interactions

E2 symbol	E2 Common name		Helix-1		Loop L1		Loop L2
*UBE2D3	UbcH5c	1	MA-LKRINKELSDLARD	:57	PTDYPFKPP	:91	SQ----------WSPA----------LT

***** Interface residues of UBE2D3 are P25, V26, Q34, T36, V49, F51, T70, T71, Y145, A146 and M147 which are out of helix-1, loop L1 and loop L2 regions.

Table S3 List of protein complexes in the template dataset

Template name	PDB code
UBE2D2/CNOT4 complex	1ur6:AB
Baculoviral IAP repeat-containing protein 3/ UBE2D2	3eb6:AB
Signal transduction protein C-cbl/UBE2L3 complex	1fbv:AC
Ubiquitin-HECT(NEDD4L)/ UBE2D2 complex	3jw0:AC
Ubiquitin-HECT(NEDD4L)/ UBE2D2 complex	3jvz:AC
TNF receptor-associated factor 6 (TRAF6)/UBE2N complex	3hct:AB
STIP1 homology and U-Box containing protein 1 (CHIP)/UBE2D1 complex	2oxq:AC
Ubiquitin-protein ligase Ube3a (E6AP)/UBE2L3 complex	1c4z:AD
U-box domain of human E4B ubiquitin ligase/UBE2D3 complex	3l1z:AB

Table S4 Target proteins and their PDB codes.

E2 and E3 proteins, for which possible interactions can be predicted by Prism, are labeled with *. For these E2 and E3s, ubiquitination activity (either mono-ubiquitination or multi-ubiquitination or poly-ubiquitination with chain-linkage preferences) are provided with references if observed in previously published studies.

Protein name	**PDB codes**	
	E2	
		Ubiquitination activity
UBE2B*	1jas	Poly-Ub (Lys11, Lys48, Lys63) [32] Mono-Ub
UBE2C*	1i7k:A	Poly-Ub (Lys11, Lys48) [33]
UBE2D1*	2c4p:A	Poly-Ub (Lys11, Lys48, Lys63) [34] Mono-Ub [31]
UBE2D2*	2esk 3jw0:B 3jvz:B 1ur6:A	Poly-Ub (Lys48) [32] Mono-Ub [31]
UBE2D3*	1x23:A	Poly-Ub (Lys11, Lys48, Lys63) [33, 35] Mono-Ub [31]
UBE2E1*	3bzh	Poly-Ub (Lys48) [32, 36] Mono-Ub [31]
UBE2E2*	1y6l:A	Poly-Ub (Lys11, Lys48, Lys63) [32, 37] Mono- Ub [31]
UBE2F*	3fn1:B	NEDD8-conjugation [38]
UBE2G1*	2awf	Poly-Ub (Lys48, Lys63) [32, 39]
UBE2G2*	3h8k:A	Poly-Ub (Lys48) [40]
UBE2H*	2z5d:A	Poly-Ub (Lys11, Lys48) [32, 41]
UBE2I*	2grn:A	SUMO-conjugation [42]
UBE2J2*	2f4w:A	Poly-Ub (Lys48) [43]
UBE2L3*	1c4z:D 1fbv:C	Poly-Ub (Lys11) [32]
UBE2L6*	2kjh:A	
UBE2M*	2nvu:C	NEDD8-conjugation [44]
UBE2N*	3hct:B 3hcu:B	Poly-Ub (Lys63) [45]
UBE2Q1*	2qgx:A	
UBE2Q2*	1zuo:A	Poly-Ub (Lys48) [32]
CDC34*	2ob4	Poly-Ub (Lys48) [46]
UBE2S*	1zdn:A	Poly-Ub (Lys11) [34]
UBE2U	1yrv:A	
UBE2W	2a7l:A	
UBE2K*	1yla:A	Poly-Ub (Lys48) [47]
	RING-finger domain type E3	
Mdm2*	2vje:A 2hdp:A	Poly-Ub, [48] Mono-Ub [48]
C-cbl*	1fbv:A 2k4d	Poly-Ub, [49] Mono-Ub [50]
Cblb	2ooa:A 2oob:A 2jnh 2do6:A	
Park2	2jmo 1iyf	
Siah1	2a25:A	
Pml	1bor	
Traf6*	3hct:A 2eci 2jmd	Poly-Ub, [51] Multi-Ub [52]

Pirh2	2k2c:A 2jrj	
Birc2	3d9t:A 3m1d:B 3d9u:A 1qbh	
Birc3*	3eb6:A	
Xiap*	2ecg	
Pias1	1v66	
Pias2	2asq:B	
Aire	2kft:A 2ke1:A 1xwh	
Brca1*	1jm7:A	Poly-Ub, [31] Mono-Ub [31]
Mid1	2jun 2dq5 2ffw	
Trim32	2ct2	
Trim37*	3lrq:A	Poly-Ub [53]
Rbx1*	3dpl:R	Poly-Ub, [54] Multi-Ub [55]
Rbx2*	2ecl	Poly-Ub [56]
	HECT domain type E3	
Ube3a*	1c4z:A 1d5f:A	Poly-Ub, [57] Multi-Ub [58]
Smurf2*	1zvd	
Itch	2nq3 2ysf 2dmv	
Wwp1*	1nd7	Poly-Ub [59]
Nedd4l*	2oni 3jw0:D 3jvz:D	Mono-Ub [60]
Nedd4	3b7y:A	
Huwe1*	3g1n:A	Poly- Ub [61]
Ubr5	1i2t 2qho:B	
Herc2	3kci	
	U-box domain type E3	
Ube4a*	1wgm	
Ube4b*	3l1x 3l1z:B 2kre	
Ppil2	1zkc:A	

Table S5. Negative E2-E3 pairs and E2-E3 pairs that could not be predicted by Prism algorithm

E2-E3 pairs which are known to be negative (i.e. non-interacting) in ubiquitination are obtained by a literature survey. Further known E2-E3 interactions that could not be predicted by Prism are obtained from literature using String search tool, which provides interactions from experiments and databases along with a confidence score (medium confidence score>0.4 is selected).

E3	E2	Reference number
Negative pairs		
Brca1	UBE2B	31
Brca1	UBE2C	31
Brca1	UBE2F	31
Brca1	UBE2G1	31
Brca1	UBE2G2	31
Brca1	UBE2H	31
Brca1	UBE2J2	31
Brca1	UBE2M	31
Brca1	UBE2Q1	31
Brca1	UBE2Q2	31
Brca1	CDC34	31
Brca1	UBE2S	31
Brca1	UBE2L6	31
Traf6	UBE2B	8
Traf6	UBE2C	8
Traf6	UBE2H	8
Traf6	CDC34	8
Ube3a	UBE2C	26
Ube3a	UBE2M	26
Xiap	UBE2B	8
Xiap	UBE2C	8
Xiap	UBE2H	8
Xiap	CDC34	8
Xiap	UBE2L3	8
Known pairs that could not be predicted		
Brca1	UBE2D1	31
Brca1	UBE2D2	31
Brca1	UBE2D3	31
Brca1	UBE2E1	31
Brca1	UBE2E2	31
Brca1	UBE2K	31
Brca1	UBE2L3	31
c-Cbl	UBE2G1	62
c-Cbl	UBE2G2	62
c-Cbl	UBE2M	63

Nedd4l	UBE2E1	[15]
Xiap	UBE2D1	[64]

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